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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,990	03/15/2004	Aaron B. Kantor	4220-99	3053
22442	7590	02/07/2007		
SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202			EXAMINER CHEU, CHANGHWA J	
			ART UNIT	PAPER NUMBER
			1641	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/07/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/801,990

Applicant(s)

KANTOR ET AL.

Examiner

Jacob Cheu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16, 18-20, 22, 24, 25, 29 and 53-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16, 18-20, 22, 24, 25, 29 and 53-58 is/are rejected.
- 7) ☒ Claim(s) 16, 20, 22 and 54, 57 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/21/2004</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment filed on 1/16/2007 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 1-15, 17, 21, 23, 26-28, 30-52 are cancelled.
2. Claims 53-58 added to the instant application.
3. Claims 16, 18-20, 22, 24-25, 29 and 53-58 are under examination.

Specification

It is noted that applicant refers the markers for diagnosing rheumatoid arthritis in Tables 1-2 using GenBank Accession numbers. The amino acid sequence is considered essential subject matter for assessing patentability of the instant invention. Each protein may have different name in different laboratories. Each protein may have different species within its family. It is known that accession number also subject to changes from time to time due to new discovery or correction. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Objections

2. Claims 16, 20, 22 and 54, 57 are objected to because of the following informalities: the hypothetical protein DKFZp434.1818.1-human (fragment) and gelsolin (amyloidosis, Finnish type). The use of parenthesis "()" is objected because it is not clear whether the "fragment" or "amyloidosis, Finnish type" is essential material necessary for the practice of the claim. It is not clear whether applicant intends to include these features into the claim. Appropriate correction is required.

Similarly as discussed in the Objection of Specification, the essential materials of amino acid sequence are necessary for practice the instant invention. Therefore, each marker needs to incorporate amino acid sequence.

Claims 24 and 29, the RA should be spelled out, or alternatively applicant can designate this abbreviation first after "rheumatoid arthritis" in claim 16.

Claim Rejections - 35 USC § 112

Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 16, 19-20, 22, 24-25, 29 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See

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Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. As held in *Brenner v. Manson*, “[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.” See 383 U.S. 519, 536 (1966).

Hypothetical Protein

As recited in the claims, the “hypothetical” protein DKFZp434P1818.1-human(fragment)” does not convey to one ordinary skill in the art what are the metes and bounds of this protein. Particularly, there is no definition of what “hypothetical” means in the specification. Examiner refers to the Webster’s II New Riverside University Dictionary, the definition 1. of, *relating to* or based on a hypothesis; 2. conjectural: suppositional; 3. contingent: conditional (See page 604). Based on the “relating to” definition, it imposes uncertainty with respect to the boundary of this marker in relation to the “hypothetical” protein. It is not known, particularly from the specification, what constitutes “relating”, e.g. homology, fragment, or some other criteria. As held in *Brenner v. Manson*, the reward is not for a hunting license for the search, but compensation for its successful conclusion. Supra. Applicant does not submit sufficient information to convey to one artisan as to the possession of this feature.

“As similar to KIAA1902 Protein”

Similarly, the term “as similar to KIAA1902”, also impose uncertainty as to the boundary of the marker. Again, applicant does not define or provide example with respect to the “similar” term in the specification. One artisan would not know what similar means or how “similar” constitutes “similarity”. Applicant does not submit sufficient information to convey to one artisan as to the possession of the invention.

“reference value”

It is noted that applicant using RA patients and healthy patients for the study of the potential diagnosis markers (See Section 0197, 0198 and 0207)(emphasis added). No other non-healthy group, e.g. other non-RA disease such as cancer, diabetes, high blood pressure, pregnancy, ...etc., was used for comparison. Applicant is entitled to what the clinical data concluded, namely “reference value from healthy control”, nothing more.

Scope of Enablement
“reference Value”

5. Claims 16, 18-20, 22, 24-25, 29 and 53-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a healthy reference, does not reasonably provide enablement for any reference. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The instant invention directs to using a plurality of marker as a diagnostic tool for rheumatoid arthritis (RA) disease. The method comprises collecting serum samples from both RA and normal population and digesting with trypsin and analyzing with mass

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spectrum techniques to identify changes in different potential protein markers (See Example 2 and Table 1). However, in view of the information and working example provided in the specification, the instant invention merely provides example for comparing RA patients with a reference value from healthy population. No other “reference” group is provided. The RA disease is complex with its etiology and pathological development. The unpredictability in the field is high. Furthermore, there are hundred or thousand diseases other than RA, and each disease has unique pathological development and etiology. It would inevitably impose undue experimentation to one artisan in the field as to how to use the recited invention as to compare with reference groups other than healthy controls.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 16, 18-20, 22, 24-25, 29, 53-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 16, step (b), line 5, the term “hypothetical” protein DKFZp434P1818.1-human (fragment) is vague and indefinite. It is not clear what constitutes “hypothetical”. Note, as discussed above, no definition is given in the specification. Is it the “exact same” or “relating to”? Similarly, claims 20, 22 and 54 suffer the same problem.

With respect to claim 16, step (b), line 7, “similar to KIAA1902” is vague and indefinite. It is not clear how “similar” this maker has to be. There is no clear metes and bounds and no definition of the degree of similarity. Similarly, claims 20, 22 and 55 suffer the same problem.

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With respect to claim 16, step (b), line 7, “similar to KIAA1902 [Homo sapiens]” is vague and indefinite. The use of “[]” is confusing. This practice is for amending claim for deletion. It is not clear what exactly applicant intends to recite in the claim language. Similarly, the use of bracket “[]” for leucine-rich alpha-2-glycoprotein [Homo sapiens], gelsolin [Homo sapiens] and lumican [Homo sapiens] in the same claim and in claims 20, 22, 55-57 suffer the same problem. Applicant need to clarify.

With respect to claim 16, step (b), “leucine-rich” alpha-2 glycoprotein is vague and indefinite. The specification has no definition what constitutes “rich”, e.g. what percentage in the overall alpha-2 glycoprotein. Similarly, claims 20, 22 and 56 suffer the same problem.

With respect to claim 16, step (c), the term “reference value” is not clear whether it is from healthy control or from non-RA disease patients, e.g. cancer or diabetes.

With respect to claim 24, “the standard level” lacks antecedent basis.

With respect to claim 24, the “reference range” lacks antecede basis.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 16, 24-25, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable by Winchester et al. (US 20050202005) in view of Dwek et al. (US 4659659).

It is noted that the instant invention, albeit recited determining a plurality of markers in step (b), nevertheless step (c) recites comparison the level of at least one of the plurality of markers to a reference value (emphasis added).

Accordingly, the instant invention can also be interpreted as using one marker for diagnosing rheumatoid arthritis (RA) disease.

Winchester et al. teach using biological samples, i.e. synovial tissues, from both the RA and the osteoarthritis patients, to determine the difference of gene expression within these two groups. Winchester et al. disclose that lumican protein are significantly overexpressed in the RA patients compared to that of osteoarthritis patients (See Figure 4; Section 0061 and 0119). However Winchester et al. do not explicitly teach diagnosing RA.

Dwek et al. teach a measuring a marker, i.e. galactosylation of an IgG component or fragment thereof, from the plasma, serum or synovial fluid from RA, osteoarthritis and normal subjects. Dwek et al. disclose all three populations have

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different levels of IgG and the results can be used for diagnosis purpose (Col. 5, line 40-55).

It would have been obvious to one ordinary skill in the art at the time the invention was made to measure the level of lumican protein in biological samples from suspected RA patients as taught by Winchester et al., and compared to a reference value, i.e. non-RA osteoarthritis patients, as taught by Dwek et al. for diagnosis RA purpose because it has been shown that lumican is significantly overexpressed in the RA patients compared to non-RA osteoarthritis patients and one ordinary skill in the art such as Dwek et al. would have been motivated to apply for diagnosis because the discrepancy of the protein markers appears in RA and osteoarthritis.

With respect to claims 24-25, it is apparent from the results of Figure 4 where the overexpression of lumican in RA is more than 3-4 fold greater than that of osteoarthritis patients.

11. Claims 16, 18-19, 53 are rejected under 35 U.S.C. 103(a) as being unpatentable by Chard et al. (Annals of Rheumatic Diseases 1988 Vol. 47, page 665-671) in view of Dwek et al..

With respect to claims 16 and 53, Chard et al. teach method of assessing the RA patients by detection of a plurality of biomarkers, including alpha-1-antichymotrypsin (ACT), C reactive protein, orosomucoid (See Abstract). Chard et al. collected serum samples from the RA patients and measured the different biomarkers. The results show that the serum concentration of ACT does correlate with the activity of RA as indicated by both clinical and laboratory parameters (See page 669, left column, Discussion). However Chard et al. do not explicitly teach comparing the level of serum of ACT to a "reference" value for diagnosis.

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Dwek et al. teach a measuring a marker, i.e. galactosylation of an IgG component or fragment thereof, from the plasma, serum or synovial fluid from RA, osteoarthritis and normal subjects. Dwek et al. disclose all three populations have different levels of IgG and the results can be used for diagnosis purpose (Col. 5, line 40-55).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have measured the level of ACT in RA patients as taught by Chard et al. with comparison to the a “reference” value, e.g. normal or osteoarthritis, as taught by Dwek et al. for the purpose of diagnosis because both articles are in analogous field, i.e. rheumatoid arthritis research, and compare a particular marker in a specified disease with a “reference value” for diagnosing purpose is well-known, widely practiced in the medical field and one artisan in the art would have been motivated to compare both RA with reference samples with reasonable expectation of success.

With respect to claims 18-19, Chard et al. teach using serum sample from RA patients. Surpa.

12. Claim 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over as Chard et al. in view of Dwek et al., and further in view of Winchester et al..

Claim 20 recites measuring at least two markers for diagnosing RA in a subject.

As discussed above, Chard et al. already taught measuring a plurality of potential biomarkers, and correlates ACT to RA (See Abstract and Table 1). However, Chard et al. do not explicitly teach two markers, e.g. ACT and lumican, for diagnosing RA.

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Winchester et al. teach lumican protein is overexpressed in RA patients. Supra.

Dwek et al. teach comparing RA with reference group for diagnosis purpose. Supra.

It would have been obvious to one ordinary skill in the art at the time the invention was made to have combined measuring two markers such as lumican and ACT as taught by Winchester and Chard et al., respectively, and comparing to a reference as taught by Yu et al. for diagnosis because lumican was found to be effective biomarker besides ACT, and using plurality markers in assessing RA is known as taught by Chard et al., thus one artisan in the field would have motivated to combine both biomarker for more thorough and efficient diagnosis.

Conclusion

13. No claim is allowed.

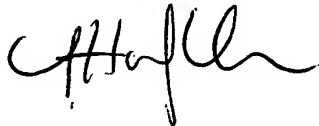
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814.

The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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A handwritten signature in black ink, appearing to read 'Jacob Cheu', with a stylized, cursive script.

Jacob Cheu
Examiner
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February 1, 2007